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AMŒBIASIS.

Nomenclature.

THE term "amœbic dysentery" was used in the past to describe infection with *Entamœba histolytica*, but since this infection does not necessarily cause dysentery, "amœbiasis" is a more suitable name, and more likely to promote correct diagnosis. Similarly, the term "tropical abscess" is somewhat misleading; for amœbic infection is not confined to the tropics, and the lesion caused in the liver is a special type of necrosis due to enzymes from the amœbæ and should not be confused with an ordinary pyogenic abscess.

Incidence.

Amœbiasis is uncommon in Australia and most of the cases that do occur are confined to people who have been outside this continent. If a person contracts the disease without having left Australia, his case history is still considered worthy of report in the medical Press, but the number of these reports is becoming large.[1,2,3,4,5,6,7,13] The data concerning carriers of amœbæ amongst the Australian population are still very meagre; the incidence was 5% amongst 500 people examined in north Queensland in 1921[11] and approximately 2% in a recent preliminary survey in New South Wales. These figures may be compared with 5% for England, 15% for the United States, and 15% to 60% for India, but it must be remembered that there are several sources of error in all such surveys: the people sampled may not be representative; the number examined may not be sufficient; the specimens taken from each individual may be too few; and the technique of the examination may not be adequate.

Even when an amœba survey has been carried out satisfactorily, it is not easy to assess the significance of the results. It is generally believed that most carriers of *Entamœba histolytica* have at least some lesions in the intestine; but it is quite certain that these lesions do not always produce symptoms. Manson-Bahr regards amœbiasis as a chronic endemic disease and believes that "it is not anything like the danger it is stated to be".[18] It was not a major medical or surgical problem in the last war, though some soldiers developed infections which were disregarded for years until amœbic hepatitis occurred. In the present war there have been at least two reports of the incidence of amœbiasis amongst troops, the one giving an account of seven patients in the Northern Territory of Australia,[7] and the other referring to 36 patients admitted to a base hospital in the Middle East.[4] There are, as yet, no published figures regarding the frequency of the disease amongst servicemen in New Guinea, though it is known to occur endemically in that area. For example, in 1937 Koller reported that amœbiasis was widely disseminated amongst both natives and Europeans at Finschhafen; a search for parasites revealed an infection rate of about 50% amongst some 300 subjects examined.[9]

From the foregoing it may be concluded that infection with pathogenic amœbæ is not an important hazard at the present time, but this view is not held in the United States. In that country there is still a vivid memory of the Chicago epidemic of 1933 in which over 1,400 victims were infected and the early death rate reached the surprisingly high figure of 7%. The incidence of carriers in the United States is high, especially in the southern part of the country, and amœbiasis is regarded as an important problem of public health. This opinion is supported in a recent article in which it was claimed that some twenty to twenty-five million people in the United States are infected with *Entamœba histolytica* and that about one million of them may probably be expected to develop hepatic complications.[12]

Even if amœbiasis is unlikely to become a major problem to our fighting forces as a whole, it will certainly occur frequently in particular areas, and, since the treatment of it is effective, medical officers should be prepared to make the correct diagnosis. The areas in which the disease is especially prevalent are India, Thailand, China and the Philippines.

Parasitology.

Entamœba histolytica is a protozoon, the vegetative form of which normally lives in the mucosa of the large intestine of man, obtaining its food by the ingestion of red blood cells. On occasions it may be carried to other parts of the body, especially to the liver, but also to such regions as the lungs, brain, kidneys and skin. Invasion of body tissues is due partly to the ability of the organism to progress by pseudopodic movements and partly to the production of an enzyme which digests the host's tissues and in virtue of which the adjective "*histolytica*" is applied to the parasite.

The vegetative forms may multiply by fission, but some fully grown amœbæ interrupt this cycle by encystment. Amœbic cysts discharged in the fæces are able to live for about ten days if kept cool and moist, but vegetative forms under the same conditions quickly succumb. The cyst is therefore the form in which the parasite is transmitted to a fresh host.

Transmission.

There are several possible methods by which the cysts may be transferred from infected fæces to a new host: (*a*) the pollution of drinking water; (*b*) the contamination of vegetables by the use of human excreta as a fertilizer; (*c*) transmission through food which has been handled by carriers of the disease; (*d*) direct contact with a carrier; and (*e*) transmission by filth flies from contaminated fæces to food.

Contamination of drinking water was responsible for the Chicago epidemic of 1933. A condenser system associated with the air conditioning plant of two large hotels was cooled by water from the city supply. This water was then run into storage tanks and used for

drinking. A cross-connexion had been provided, however, between the main sewer and the outlet pipe from the condenser, so that if the storage tank became full, excess water could be diverted into the sewer. At the time in question the air conditioning system was undoubtedly overloaded, because the weather was hot, and over seven million people had gathered in the city to see a World Progress Exhibition. There is evidence that the connexion between the sewer and the water system was opened and was subsequently closed incompletely. Owing to the fact that there was a slight drop in hydrostatic pressure between the sewer and the water pipe, contamination of the drinking water took place.

A further epidemic occurred in Chicago in 1934 when several people, who had been helping to control a city fire, drank water from an unfiltered supply. This provided the second definite instance of an outbreak of amœbiasis due to the drinking of infected water. It had previously been considered that food handlers were usually responsible for the transmission of the disease. The incrimination of drinking water is very important, for it gives the clue to the explanation of the prevalence of amœbiasis in certain rural areas; moreover, it provides a warning as to what could readily happen in an army camp—a warning which is made more necessary by the fact that chlorination of water does not destroy amœbic cysts.

The other methods of transmission vary in importance. In the East fertilization of vegetables is carried out with human excreta. As for filth flies, they do not commonly carry cysts externally, but the cysts remain viable for as long as three and a half hours after they have been ingested and excreted.[11]

Pathology.

The *Entamœba histolytica* multiplies in the submucous layer of the large intestine, and causes necrosis of the surrounding tissues and thrombosis of the small venules. If the overlying mucous membrane sloughs away, an ulcer is formed; such a process most commonly occurs in the upper reaches of the large intestine.

The amœbæ may spread from the primary focus in the intestine through the portal vein to the liver. If they reach the liver in sufficient numbers to cause thrombosis and infarction, a microscopic area of necrosis is established and this is enlarged by the cytolytic activity of the organism. In many instances the early lesion does not progress, but is healed by connective tissue replacement.[12] It is possible that factors such as previous hepatitis help to determine whether the process will remain localized. If the small foci increase in size they eventually fuse and produce an amœbic abscess. Owing to the fact that most of the intestinal lesions are found in the caecum and ascending colon, the majority of the amœbæ that go to the liver proceed via the branches of the superior mesenteric vein, the blood from which maintains its identity in the portal stream and is distributed chiefly to the right lobe of the liver. Consequently, it is not surprising to find that 80% of amœbic abscesses are also found in the right lobe.

The appearance of the abscess varies with its age; at first it is a small greyish-brown moth-eaten area, but it may enlarge to a diameter of six to eight inches and acquire a hard fibrous wall. The contents of the developed abscess consist of blood, cytolyzed tissue and liver parenchyma, and have been described as resembling chocolate sauce. Characteristically, this pus is sterile, but occasionally it becomes infected with staphylococci, streptococci, enterococci, colon bacilli, anaerobes, *Bacillus pyocyaneus* or pneumococci. Amœbæ are present in the wall of the cavity, but cannot be demonstrated in the pus until the abscess has been tapped on a second occasion. This has been explained by the suggestion that the low oxygen tension in the original pus prevents the amœbæ from surviving, but the cavity becomes aerated when the contents are first withdrawn, and subsequently live parasites may be found in the pus. Strangely enough amœbic cysts are never found in the liver.

When a large amount of liver tissue is destroyed, compensatory hypertrophy of the remainder may occur. In this way the liver is able to accommodate as much as six pints of pus—a relatively enormous quantity, which occupies one and a half times the normal hepatic volume.

Most of the amœbæ that are disseminated through the portal system are filtered out by the liver. Experimentally it is difficult to produce a lesion in any organ except the liver when amœbæ are injected into the portal vein of a kitten.[13] In man, however, it is possible for some parasites to pass on and settle in the lungs, brain, renal tract and possibly other situations. Spread of the disease can also occur by the rupture of an amœbic abscess of the liver. Owing to the proximity of the usual abscess to the right dome of the diaphragm, 50% of the ruptures occur into the thorax; in a further 25% the pus passes into the peritoneal cavity, and in the remainder the structures involved include the pericardium, stomach, intestine, *vena cava*, kidney and bile duct.

Clinical Features.

The clinical features of amœbiasis have been divided into the following groups, which will be discussed in turn:

1. Asymptomatic infections.

2. Symptomatic infections: (*a*) slight and vague illness; (*b*) chronic illness resembling chronic appendicitis, peptic ulcer or chronic cholecystitis; (*c*) diarrhœa or dysentery; (*d*) hepatitis.

The patients, of course, do not show a fixity of symptoms, but may change from one group to another. Moreover, the last syndrome may be coexistent with one of the others.

Asymptomatic Infections.

Although it is believed that all carriers have lesions in the large bowel, there are many who are not troubled by symptoms.

Symptomatic Infections.

Slight and Vague Illness.—When slight or vague illness is present the patient's condition is only slightly worse than that of a carrier. Such symptoms as he has are referred to the gastro-intestinal tract. They include a tendency to constipation, vague abdominal pain and mild toxæmia. Subjects with slight symptoms, or none at all, make up about 50% of the people infected with pathogenic amœbæ.

Chronic Illness Resembling Chronic Appendicitis, Peptic Ulcer or Chronic Cholecystitis.—When the lesion is localized to the caecum there is usually no tendency to diarrhœa, but the chronic inflammation causes a pain which, according to its distribution, is mistaken for a symptom of chronic appendicitis, peptic ulcer or chronic cholecystitis. The associated symptoms which are held to suggest one or other of these diagnoses include low-grade pyrexia, loss of weight, anorexia, nausea, vomiting, acid eructations and heartburn. Sometimes, perhaps after a period of years, the lesions extend and one of the remaining syndromes is precipitated.

Diarrhœa or Dysentery.—The incubation period varies from a week to several months and is terminated by an abrupt onset of the disease. The closer the lesions are to the rectum, the more likely is there to be looseness of the bowels. The dysentery is generally less urgent than in the bacillary type, but this is not an absolute point of distinction. The stools number perhaps three to ten daily and usually consist of blood and sloughs mixed with fæces, the whole resembling anchovy sauce. Sometimes the stools may be merely soft and flecked with blood and mucus. Fever may be absent as long as the liver is not secondarily infected, but if, as sometimes happens, the acute dysentery is associated with hepatitis the patient may have a temperature of 103° to 105° F. and show marked prostration. The caecum is often thickened and tender.

Hepatitis.—This usually commences insidiously as an unexplained pyrexia, but it may have an acute onset. Although preceding diarrhœa, when present, is a very useful guide to the diagnosis, it must not be expected to feature in every patient's history. The interval between the dysentery and the hepatitis is usually two or three

months, but may be many years. The liver is generally enlarged, and if the hepatitis is superficial there may be hepatic pain, tenderness and epigastric discomfort.

The hepatitis may progress to a frank amœbic abscess. The clinical aspects of the latter are so important that they will be discussed separately below.

Clinical Features of Amœbic Abscess of the Liver.

The patient may complain of hepatic pain and tenderness, loss of weight and energy, flatulent dyspepsia, constipation interrupted by periodic looseness of the bowels, irritability and insomnia. He has a sallow, earthy complexion, or even jaundice; he has a coated tongue and moderate anæmia; and his liver is enlarged and tender. The temperature at first merely rises slightly in the evening, but later there is intermittent fever with considerable sweating. Rigors may occur, especially if there is secondary infection of the abscess.

Further clinical features differ according to the position of the abscess. (*a*) An abscess in the upper right half is liable to press on the diaphragm and cause referred pain in the right shoulder and signs at the base of the right lung such as diminished breath sounds and crepitations. If the abscess ruptures through the diaphragm it gives rise to pulmonary infection which may lead to hæmoptysis. When the lesion communicates with a bronchus, the patient may cough up large quantities of pus which resembles chocolate sauce. (*b*) An abscess in the lower right half of the liver causes marked downward enlargement of that organ and may even bulge into the right loin. The patient complains of a feeling of weight when walking; he may attempt to splint his liver by supporting the affected part with his arm and forearm, or by sleeping on the affected side, or by muscle guarding with his right rectus muscle. (*c*) An abscess in the left half of the liver may cause gastric disturbances, and may present in the epigastrium. Rupture may occur into the stomach, the pericardium, or the left side of the thorax.

Diagnosis of Dysentery due to Entamœba Histolytica.

Clinically, the diagnosis is suggested by persistent or relapsing diarrhœa, with characteristic offensive stools which contain fæcal matter and resemble anchovy sauce. The clinical features, however, are often inconclusive or misleading, and the diagnosis depends finally on the demonstration of *Entamœba histolytica* in the fæces or in scrapings obtained from an ulcer through a sigmoidoscope. The parasite is in the form of trophozoites during the acute stages and this is the form which is usually present in liquid fæces, though cysts may sometimes be identified as well. If the stools are formed the examiner should look for cysts. As a general rule trophozoites are more difficult to identify than cysts, and serious errors can be made in detecting them unless the stool is fresh and warm when examined. On the other hand, there are more trophozoites in an average liquid specimen than there are cysts in an average formed specimen.[9] When experienced workers examine a liquid stool for trophozoites, they can detect about 80% of the positive cases by a single examination, 95% by two examinations and almost all by three examinations.[9] When they are searching for cysts in formed stools, however, only 20% of the positive cases can be detected by a single examination of a stained fæcal film. If the examination also includes a specimen concentrated by the zinc sulphate centrifugal flotation technique, about 30% are detected in a single examination and 70% to 90% in five examinations.[35] Because of the better results which skilled workers obtain from a liquid specimen, it is quite common to give a saline cathartic to the subject on the morning of the examination in order to obtain unformed fæces.

The search for vegetative forms must be carried out as soon as the stool is passed, for movement of the amœbæ is an important diagnostic feature, and this movement is lost in about half an hour if the stool is not maintained at body temperature. Further, the specimen should be obtained free of urine, for urine obscures details of structure. A preparation is made by mixing a small amount of fæces with warm water or saline solution and spreading it into a film on a slide. The film should be homogeneous and sufficiently thin to permit one to read newsprint through the slide. A warm stage is not essential, but if some heat is supplied by an electric light, the chances of detecting movement are improved.

The specimen is examined under reduced illumination so that advantage can be taken of the refractile nature of the amœbæ. The examiner must be sufficiently expert to detect the organisms in the first instance by use of the low-power lens (2/3 inch objective and × 10 eye-piece, giving a magnification of 100 diameters). They show up as refractile specks. All suspicious objects have to be examined critically under the high-power lens. The chief features in the diagnosis are as follows: (*a*) The amœbæ move in a definite direction by pseudopodic progression. (*b*) Red blood cells may be seen within the cytoplasm; large mononuclear cells may also ingest erythrocytes, but mononuclears are non-motile. (*c*) The ectoplasm is seen as a clear rim around the granular endoplasm; the nucleus is difficult to detect, but one can sometimes distinguish a peripheral zone of chromatin and, more rarely, a central delicate karyosome. The nucleus can be made apparent by running a small amount of Lugol's iodine beneath the cover slip, though the iodine, of course, kills the organism.

Non-pathogenic amœbæ do not ingest erythrocytes and they quickly lose their motility; only rarely, in a fresh preparation, can their nuclei be seen.

Cysts can be searched for in fresh material, which may either be examined directly or concentrated before examination, but their distinctive characteristics are best seen if the specimen is stained with Lugol's iodine. They are spherical structures containing several nuclei, two or three chromatoid bodies in the form of rods, and, sometimes an aggregation of glycogen. The cysts of *Entamœba histolytica* have four nuclei, whereas those of the non-pathogen, *Entamœba coli*, have eight. Other non-pathogens, however, have four nuclei and so has *Entamœba coli* at one stage of its development. Therefore the final basis on which *Entamœba histolytica* is diagnosed is the structure of the nucleus—the fine peripheral beaded chromatin and the central minute karyosome.

Diagnosis of Amœbic Abscess of the Liver.

The clinical diagnosis of amœbic abscess of the liver depends on the presence of the following rather constant features: pain and tenderness in the hepatic area; enlargement of the liver; pyrexia of moderate degree; and, in about 50% of the patients, a history of antecedent diarrhœa. The evidence obtained from the presence or absence of these features is reinforced by the following investigations.

1. An attempt should be made to demonstrate active or encysted forms of the amœbæ in the fæces. Inability to find the parasite does not invalidate the diagnosis.

2. A sigmoidoscopic examination should be made to detect amœbic ulceration. Usually the examination is unsuccessful, for the ulcers do not often extend down as far as the sigmoid colon. If an ulcer is seen it is gently curetted and the scrapings are examined microscopically for amœbæ.

3. Radiographs should be taken to reveal the condition of the lung and diaphragm. Abnormal findings include: elevation of the diaphragm on the affected side; localized bulging of the diaphragm; diminished movement of the diaphragm; and signs at the base of the adjacent lung indicative of collapse, consolidation, effusion or abscess.

4. Total and differential leucocyte counts should be carried out. In uncomplicated amœbic abscess of the liver there is typically a moderate leucocytosis of 10,000 to 20,000 cells per cubic millimetre. If the abscess becomes infected with pyogenic organisms the total count often rises to more than 20,000 and the polymorphonuclear leucocytes constitute 85% or more of the whole.

5. If there are reasonable grounds for suspecting the presence of amœbic hepatitis or liver abscess, but definite proof is lacking, the patient may be given a course of emetine. The diagnosis is confirmed if the temperature returns to normal in seventy-two hours, though this

response will not be obtained if the abscess is secondarily infected.

6. The final diagnostic step for liver abscess is the aspiration of pus. The commonest site for an abscess is in the right lobe near the dome. Therefore if there is no guide, such as pointing or localizing signs, to indicate the probable site, an aspirating needle should be inserted in the eighth or ninth intercostal space in the anterior axillary line and pushed inward, backward and slightly upward. If pus is not obtained the needle is withdrawn and passed in a different direction; otherwise extensive damage can be done to the friable liver substance. When the abscess is believed to be anterior, the needle is introduced just below the anterior costal margin about four to six centimetres lateral to the mid-line, and is directed superiorly and posteriorly. If the suspicion is that the abscess lies posteriorly, the needle is inserted in the right lumbo-costal angle and directed superiorly and anteriorly.[22] It must be remembered that there are two important dangers in this procedure—hæmorrhage and extension of pyogenic infection. Hæmorrhage usually comes from congested vessels in the liver, and therefore previous administration of emetine for two days makes the complication less likely. Another protective measure is the use of a needle with a length of not more than 9·0 centimetres and a diameter of not more than 2·0 millimetres; such a needle will not damage the liver tissue too much and will not reach the inferior *vena cava* in a man of average size. The exploration should be carried out in an operating theatre under local anæsthesia. Nicking the skin with a scalpel at the contemplated site of puncture facilitates insertion of the needle.

Treatment of Acute Amœbiasis.

The general treatment is fourfold: (*a*) rest in bed until four days after the course of emetine has been concluded; (*b*) the use of a diet which is easily digested and of low residue, and which does not include condiments and alcohol; (*c*) symptomatic treatment for the abdominal pain; and (*d*) the use of purgatives to treat the constipation which usually follows the initial diarrhœa.

The drugs employed are emetine and one of the organic arsenicals, of which "Carbarsone" is probably the best. Emetine is an effective but toxic drug; it is given by subcutaneous or intramuscular injection in a dose of one grain per day. On no account should this course be repeated in less than three weeks, because the body can destroy only one-third of a grain per day and the drug is therefore cumulative when given in the above dose. Emetine usually has a dramatic initial effect, but it needs to be supplemented by other therapy, because of itself it cures only about 20% of the patients; it acts primarily on organisms present in the tissues and has little action on organisms in the bowel. Toxic effects are shown on the vomiting centre, and on both cardiac and somatic muscle, and include nausea, vomiting, diarrhœa, low blood pressure, tachycardia, irregularity of the heart, and extreme muscular weakness.

"Carbarsone" is given in gelatin capsules containing 0·25 gramme of the drug, the dose being one capsule twice daily, after food, for ten days. Unlike emetine, it can be given to ambulant patients and to those with cardiac disease.

Treatment of Carriers and Patients who have Relapsed.

Emetine, given parenterally, is not effective in the treatment of carriers or patients who have relapsed, and the drugs employed are: (*a*) emetine-bismuth-iodide, (*b*) an organic iodine compound such as "Yatren" (also called "Quinoxyl" or chiniofon), "Diodoquin" or "Enteroviоform", and (*c*) an organic arsenical such as "Carbarsone".

Emetine-bismuth-iodide is given just before the patient retires. It is very liable to cause vomiting, and therefore the patient should take a light evening meal, and should be given a sedative before retiring. On the first night one grain is given, on the second two grains, and subsequently three grains, the total dose being 27 grains. Concurrently with this treatment chiniofon enemata are given. The bowel is washed out each morning with one pint of 2% sodium bicarbonate solution to remove mucous, and then a retention enema of six ounces of 2% solution of chiniofon is administered. "Carbarsone" given orally is a substitute for the chiniofon.

Treatment of Amœbic Hepatitis and Amœbic Abscess.

The course of emetine described above has a very satisfactory effect on amœbic hepatitis or amœbic abscess of the liver. In large abscesses aspiration is required in addition. The only indication for open drainage is the presence of secondary bacterial infection, and even this may sometimes be treated conservatively by aspiration and the administration of sulphonamides. In spite of the fact that "Yatren" and "Carbarsone" are said to cause liver damage, it may be necessary to give these drugs in order to remove from the intestine any amœbæ which may reactivate the lesion in the liver.[23]

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